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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,531	09/05/2003	David Baltimore	CTCH-P01-016	8769

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EXAMINER	
PATTERSON, CHARLES L JR	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,531	BALTIMORE ET AL.	
	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,18,20,21,28,40,43 and 98-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,18,20,21,28,40,43 and 98-123* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The disclosure is objected to because of the following informalities:

On page 16, line 15 and page 53, lines 3-4, the recitation of "in bold" is not understood. Applicants have changed the instant recitations from "in red" to "in bold", however looking at figure 4, there is not seen any bold nucleotides. If they perhaps did not copy correctly then applicants should submit another Figure 4.

On page 37, lines 12-13, it is stated that "[t]he rate of DSB-GT was highest when Sce expression is driven by the CBA promoter, intermediate with the CMV promoter, and lowest with the PGK promoter (Figure 2E)". Looking at figure 2E it appears that PGK is intermediate and CMV is the lowest.

Appropriate correction is required.

Claims 98 and 105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 98 and 105 are confusing in that the limitation of the instant claims is already in the claims they depend from.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 18, 20-21, 28, 40, 43, 98-123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which

it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification teaches that chimeric nucleases are "fusions between zinc finger binding DNA binding domains and the endonuclease domain of FokI restriction enzyme ('Fn')" (page 47, lines 27-29). Applicants apparently designed three different chimeric nucleases, each apparently having the Fn nuclease domain (page 48, lines 6-11). The instant claims have no limitation on the chimeric nucleases but are broadly drawn to "(i) a DNA binding domain; (ii) a cleavage domain; and (iii) a nuclear localization signal". Apparently all of the examples shown in the specification use zinc finger for the binding domain, the nuclease cleavage domain of FokI and do not have a nuclear localization signal, as discussed *infra*.

It is not seen where in the specification it is taught that a nuclear localization signal is present in the chimeric nucleases made. On page 49, lines 12-13 it is stated that "[i]f the chimeric nucleases did not have a nuclear localization signal they were unable to stimulate gene targeting (data not shown)", but apparently the placing of a specific nuclear localization signal in the chimeric nuclease is not taught in the specification. Exactly how the nuclear localization signal is placed in the chimeric nuclease nor the identity of the nuclear localization signal is not taught. On page 23, lines 3-10, it is stated that there are several types of nuclear localization signals known it the prior art, some of which are defined and some of which are not. Therefore unless applicants can point out where in the specification the addition of a nuclear localization signal to the chimeric nuclease is taught, it is maintained that applicants are not enabled for this embodiment and that undue experimentation would be required to place such a signal into a chimeric enzyme and have it be operable.

On pages 55-56, applicants discuss constructing "CD9CN1" and "CD8CN2". They then refer to Figure 13 as showing the results with these constructs. Figure 13 shows "CD8ZF1" and "CD8ZF2", not "CD9CN1" and "CD8CN2". Therefore the instant recitation and figure do not show what applicants claim they show.

It is maintained that the instant invention as claimed is not enabled by the instant specification and that undue experimentation would be required for one of ordinary skill in the art the practice the invention.

Claims 1-11, 13, 18, 20-21, 28, 40, 98-108 and 118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As noted *supra*, the instant specification apparently does not teach that a chimeric nuclease has been made with a nuclear localization signal. The results shown in Figure 3 were obtained by "co-transfecting the appropriate nuclease with the repair substrate", page 15, lines 16-17. On page 14, lines 15-16 it is taught that "transfections were performed by the calcium phosphate technique" and on page 48, line 28 it is stated that "[a]pplicants co-tranfected the chimeric nuclease with the repair substrate". Therefore, apparently the instant specification teaches cells transfected with repair substrate and nuclease using the calcium phosphate technique. This does not involve the transport of proteins across nuclear pore complexes using nuclear localization sequences. It is stated on page 49. lines 12-13 that "[i]f the chimeric nucleases did not have a nuclear localization signal they were un-

able to stimulate gene targeting (data not shown)", but that recitation is not understood as apparently applicants did not add a nuclear localization signal.

Therefore, apparently the specification does not teach or describe the addition of nuclear localization signals to the chimeric nucleases, as required in the instant claims and thus does not describe this embodiment.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 43, 109-117 and 119-123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bibikova, et al. (CA) in view of Choulika, et al. (BD). As stated previously, Bibikova, et al. teach the use of a chimeric nuclease consisting of the cleavage domain of *Fok*I and a DNA binding domain consisting of zinc fingers. In the sentence spanning pages 289-290 it is stated that "randomization of the codons for the recognition residues allows the selection of new fingers that have high affinity for arbitrarily chosen DNA sequences", and in the next paragraph it is stated that "[i]njected linear DNAs undergo efficient recombination if they carry appropriately placed homologous sequences". In the last full paragraph of column 1 on page 296 it is stated that "two new chimeric nucleases would be delivered to cells along with a linear donor DNA molecule carrying the desired sequence alteration [and that] [t]he method of delivery would depend on the organism, cell type, and other experimental conditions".

Choulika, et al. teach a method of gene repair involving introducing into the cell, a vector containing "targeting DNA flanked by a restriction endonuclease site and comprised (1) DNA homologous to chromosomal DNA adjacent to the specific sequence of interest and (2) DNA which repairs the specific sequence of interest upon recombination between said targeting DNA and the chromosomal DNA; and b) introducing into said cell a second vector comprising a nucleic acid encoding a restriction endonuclease which cleaves the restriction endonuclease site present in the first vector" (claim 1). This is essentially the method of claim 43 except that claim 43 uses a chimeric nuclease and Choulika, et al. use simply a restriction enzyme.

It would have been obvious to one of ordinary skill in the art to use the target sequence according to the method taught by Choulika, et al. and to use a chimeric nuclease as taught by Bibikova, et al., absent unexpected results. It is maintained that everything else in the instant claims would have been obvious, absent convincing proof to the contrary. The instant claims do not require a nuclear localization signal.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 571-272-0936. The examiner can normally be reached on Monday - Friday from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status informa-

tion for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
November 8, 2005